NATURAL COMBINATION HORMONE REPLACEMENT FORMULATIONS AND THERAPIES

CROSS-REFERENCE TO RELATED APPLICATIONS

This application claims priority to U.S. Provisional Application Ser. No. 62/002,090, filed May 22, 2014, the content of which is incorporated by reference herein in its entirety.

FIELD OF THE INVENTION

This application relates to pharmaceutical compositions and methods for hormone replacement therapy.

BACKGROUND OF THE INVENTION

Hormone Replacement Therapy (HRT) is a medical treatment that involves the use of one or more of a group of medications designed to increase hormone levels in women who lack adequate hormone production. HRT can mitigate and prevent symptoms caused by diminished circulating estrogen and progesterone hormones in a pre-menopausal, peri-menopausal, menopausal or post-menopausal subject.

BRIEF SUMMARY OF THE INVENTION

In one aspect, pharmaceutical compositions for co-administering estradiol and progesterone to a subject in need of natural hormone replacement therapies are provided. In some embodiments, the pharmaceutical composition comprises: solubilized estradiol, suspended progesterone, and a solubilizing agent, wherein the solubilizing agent is a medium chain (C6-C12) oil and wherein the pharmaceutical composition, when administered to a subject, produces in a plasma sample from the subject one or more pharmacokinetic parameters as described herein (e.g., an area under the curve $(AUC)_{(0-t)}$ or a C_{max} for estradiol, progesterone, estrone, or total estrone as described herein, e.g., in Tables 18-21).

In some embodiments, the pharmaceutical composition comprises a solubilizing agent that comprises a glyceride of at least one C6-C12 fatty acid. In some embodiments, the glyceride ester is a mixture of mono- and diglycerides (e.g., glyceryl caprylate/caprate). In some embodiments, the fatty acid is predominantly a C8 to C10 fatty acid. In some embodiments, the pharmaceutical composition further comprises a surfactant (e.g., lauroyl polyoxyglyceride). In some embodiments, the pharmaceutical composition comprises estradiol at a dosage of about 0.05, 0.1, 0.125, 0.15, 0.20, 0.25, 0.30, 0.35, 0.375, 0.40, 0.45, 0.50, 0.55, 0.60, 0.625, 0.65, 0.70, 0.75, 0.80, 0.85, 0.90, 0.95, 1.00, 1.125, 1.25, 1.375, 1.50, 1.625, 1.75, or 2.00 mg, and comprises progesterone at a dosage of about 25, 50, 75, 100, 125, 150, 175, 200, 250, 300, 350, or 400 mg. In some embodiments, the pharmaceutical composition comprises estradiol at a dosage of about 0.25 mg and comprises progesterone at a dosage of about 50 mg. In some embodiments, the pharmaceutical composition comprises estradiol at a dosage of about 0.50 mg and comprises progesterone at a dosage of about 50 mg. In some embodiments, the pharmaceutical composition comprises estradiol at a dosage of about 0.50 mg and comprises progesterone at a dosage of about 100 mg. In some embodiments, the pharmaceutical composition comprises estradiol at a dosage of about 1 mg and comprises progesterone at a dosage of about 100 mg. In some embodiments, the pharmaceutical composition comprises estradiol at a dosage of about 2 mg and comprises progesterone at a dosage of about 200 mg.

In some embodiments, the pharmaceutical composition comprises about 0.25 mg estradiol and about 50 mg progesterone, and administration of the composition to the subject produces, in a plasma sample from the subject, one or more parameters selected from:

(i) an area under the curve $(AUC)_{(0-t)}$ for estradiol that is from 140.3733 pg·hr/ml to 219.3333 pg·hr/ml;

(ii) a C_{max} for estradiol that is from 6.4790 pg/ml to 10.1235 pg/ml;

(iii) an $AUC_{(0-t)}$ for progesterone that is from 24.0174 ng·hr/ml to 37.5272 ng·hr/ml; and

(iv) a C_{max} for progesterone that is from 17.8444 ng/ml to 27.8819 ng/ml.

In some embodiments, administration of the composition to the subject further produces, in a plasma sample from the subject, one or both parameters selected from: an $AUC_{(0-t)}$ for estrone that is from 909.6091 pg·hr/ml to 1421.2642 pg·hr/ml; and a C_{max} for estrone that is from 42.6549 pg/ml to 66.6483 pg/ml.

In some embodiments, administration of the composition to subject further produces, in a plasma sample from the subject, one or both parameters selected from: an $AUC_{(0-t)}$ for total estrone that is from 20.1752 ng·hr/ml to 31.5238 ng·hr/ml; and a C_{max} for total estrone that is from 3.5429 ng/ml to 5.5358 ng/ml.

In some embodiments, the pharmaceutical composition comprises about 0.25 mg estradiol and about 50 mg progesterone, and administration of the composition to a subject produces, in a plasma sample from the subject, the following parameters:

(i) one or both of (a) an $AUC_{(0-t)}$ for estradiol that is from 140.3733 pg·hr/ml to 219.3333 pg·hr/ml and (b) a C_{max} for estradiol that is from 6.4790 pg/ml to 10.1235 pg/ml; and

(ii) one or both of (a) an $AUC_{(0-t)}$ for progesterone that is from 24.0174 ng·hr/ml to 37.5272 ng·hr/ml and (b) a C_{max} for progesterone that is from 17.8444 ng/ml to 27.8819 ng/ml; and optionally

(iii) one or both of (a) an $AUC_{(0-t)}$ for estrone that is from 909.6091 pg·hr/ml to 1421.2642 pg·hr/ml and (b) a C_{max} for estrone that is from 42.6549 pg/ml to 66.6483 pg/ml; and optionally

(iv) one or both of (a) an $AUC_{(0-t)}$ for total estrone that is from 20.1752 ng·hr/ml to 31.5238 ng·hr/ml and (b) a C_{max} for total estrone that is from 3.5429 ng/ml to 5.5358 ng/ml.

In some embodiments, a pharmaceutical composition for co-administering estradiol and progesterone to a human subject in need thereof comprises about 0.50 mg estradiol and about 50 mg progesterone, and administration of the composition to the subject produces, in a plasma sample from the subject, one or more parameters selected from:

(i) an $AUC_{(0-t)}$ for estradiol that is from 280.7467 pg·hr/ml to 438.6667 pg·hr/ml;

(ii) a C_{max} for estradiol that is from 12.9580 pg/ml to 20.2469 pg/ml;

(iii) an $AUC_{(0-t)}$ for progesterone that is from 24.0174 ng·hr/ml to 37.5272 ng·hr/ml; and

(iv) a C_{max} for progesterone that is from 17.8444 ng/ml to 27.8819 ng/ml.

In some embodiments, administration of the composition to the subject further produces, in a plasma sample from the subject, one or both parameters selected from: an $AUC_{(0-t)}$